AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph on page 15, line 10, to page 16, line 28, of the specification of record with the following rewritten paragraph marked-up to show changes:

In a further preferred embodiment of the present invention, the furin endoprotease activities are enzyme activities from vertebrate or more preferably mammalian furin endoprotease enzyme. Further strongly preferred, either alone or in conjunction with the immediately preceding embodiment, is that the furin endoprotease activity is a constitutive endoprotease activity belonging to constitutive secretion pathway. Such endoprotease activity has an aforementioned tetrabasic cleavage site characteristically. It must be understood in the present context that antibodies are usually secreted by constitutive secretion; regulated secretion requires sorting to a distinct subset of secretory vesicles. Furin endoproteases functioning in regulated secretion, e.g. insulin processing PC 2 and PC3, will only be active in those particular secretory vesicles; regulated secretion usually results in very large Ca influx. Sorting of protein to those distinct vesicles requires specific sorting signals, at least some of which are protein specific and poorly understood. Further, for the purpose of the present invention, it goes without saying that the level e.g. of endogenous furin/PACE activity may vary. Chinese hamster ovary cells (CHO) have comparatively low endogenous furin activity; a heterologously expressed, furin-cleavable fusion protein may be secreted up to 30-50% by CHO cells in the uncleaved, native form. Overexpression of recombinant, CHO-derived furin enzyme may help to cleave such fusion protein quantitatively. Despite overexpression, careful localization studies demonstrated that all furin activity was still properly Golgi-only localized. However, overexpression of Kex-2 activity in CHO cells, equipped with suitable secretion leader pre-sequence, has been reported to result in widespread expression of Kex-2 in the secretory pathway including the ER; unlike e.g. mammalian proinsulin convertases PC2 and PC3, Kex-2 proved to retain considerable constitutive proteolytic activity under these conditions, resulting in early cleavage in the ER. However, according to the present invention, in case of recombinant host cells only properly

Golgi-only or preferably late Golgi-only localized furin family endoprotease activity falls within the scope of the present invention. Localisation signals for proper Golgi-only localisation of active endoprotease, ionic environment and autoproteolytic activation in the ER contributing to the onset of enzymatic activity, are highly species dependent and may fail when protein is heterologously expressed in fairly distant species. Therefore in a further preferred embodiment of the present invention, the host cells according to the present invention are devoid of non-vertrebrate, more preferably non-mammalian furin endoprotease activity stemming from native endoprotease enzyme such as e.g. Kex-2 of yeast. What is possible though, is to create properly localized, artifical hybrid enzymes assembled by a localization signal moiety and an active enzyme domain; since approach may not work out simply, a more elaborate combinatorial format for creating functional variants of furin endoproteases having proper Golgi-only or late Golgi-only localization properties should be chosen. Such approach is described for the similar task of glycosylation engineering by means of precisely localized, heterologous glycosyltransferases in Choi et al., Use of combinatorial genetic libraries to humanize N-linked glycosylation in the yeast Pichia pastoris, PNAS 2003, Vol. 100: 5022-5027 and WO 02/00879. WO 02/00879 describes requirements of adequate signal sequences for Golgi localization and pH optima requirements for protease domain activity in detail; said features disclosed therein, in particular the Golgi localization sequences, are herewith incorporated to the present description. In a preferred embodiment of the present invention, suitable functional variants of the active enzymes of the furin endoprotease family according to the present invention do not encompass, i.e. are devoid of such inter-species or chimeric protease enzymes obtained by artifical combination of localization and protease domains of different species origin. - The localization/retention signal sequence of furin is also known: 711-PSDSEEDEG-780 (SEQ ID NO.: 1) (Takahashi S et al.: J Biol Chem. 1995 Nov 24;270(47):28397-401. There is also a recycling signal to transport furin from the cell membrane back into the cell, probably as a salvage mechanism making up for a minor degree leaky retention in the Golgi, thus preventing

surface display or extracellular shedding of furin. For biotechnological application, this is of course an important aspect.

Please replace the paragraph on page 24, lines 1-8, of the specification of record with the following rewritten paragraph marked-up to show changes:

The gene structure of mouse-human chimeric antibody cB72.3 is described in Whittle et al., Protein Eng. 1987, Dec. 1(6):499-505; the original hybridoma cell line B72.3 from which the recombinant chimeric antibody was constructed is obtainable from ATCC as ATCC No.HB-8108. For the purpose of the present experiment, an in-frame fusion is generated by linking the C-terminus of the light chain of cB72.3 via the sequence -Arg-Arg-Lys-Arg-(Gly-Gly-Gly-Gly-Ser)$_3$-Arg-Arg-Lys-Arg- (SEQ ID NO.: 2) to the N-terminus of the heavy chain of cB72.3, further eliminating the signal peptide coding sequence from the heavy chain coding sequence's N-terminus.

Please replace the header on page 25, line 9, of the specification of record with the following rewritten header marked-up to show changes:

Table I (SEQ ID NO.: 3)

In the Sequence Listing:

Please insert the attached Sequence Listing (pages 1-7) at the end of the specification of record.